REVIEW

Mechanical ventilation in cardiogenic shock

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Purpose of review
Mechanical ventilation is frequently needed in patients with cardiogenic shock. The aim of this review is to summarize and discuss the current evidence and the pathophysiological mechanism that a clinician should consider while setting the ventilator.

Recent findings
Little attention has been placed specifically to ventilatory strategies in patients with cardiogenic shock undertaking mechanical ventilation. Lung failure in patients with cardiogenic shock is associated with worsening outcome as well as a delay in mechanical ventilation institution. The hemodynamic profile and cardiogenic shock cause, considering the preload dependency of the failing heart, must be defined to adjust ventilatory setting.

Summary
Evidence is growing regarding the role of lung failure as adverse prognostic factor and beneficial effect of positive pressure ventilation as part of first-line treatment in patients with cardiogenic failure.

Keywords
cardiogenic shock, heart–lung interactions, intrathoracic pressure, positive pressure ventilation, respiratory failure

INTRODUCTION

Mechanical ventilation is commonly required in patients having cardiogenic shock. Despite this, there is paucity of large-scale epidemiological and clinical data of patients with acute respiratory failure (ARF) and regarding the best ventilatory strategy in this setting. In addition, datasets regarding epidemiology, pathophysiology and treatment pertain mostly patients with cardiogenic shock related to acute myocardial infarction related cardiogenic shock (AMI-CS). This review discusses knowledge regarding physiological and pathophysiological mechanism of cardio–pulmonary interaction and ventilation parameters in patients with severe hemodynamic instability, examining relevant data available in the most recent literature.

EPIDEMIOLOGY OF RESPIRATORY FAILURE IN CARDIOGENIC SHOCK

The esteemed prevalence of mechanical ventilation in patients with cardiogenic shock ranged from 43 to 88% for the management of acute hypoxemia, increased work of breathing, airway protection, and hemodynamic or electric instability [1,2▪,3–5]. In addition, a trend in a steady increase in the proportion of admissions with ARF and greater use of noninvasive ventilation (NIV) and mechanical ventilation have been described over the last 2 decades [2▪].

The wide range regarding the application of mechanical ventilation in cardiogenic shock can be explained by the vast heterogeneity in the definition of cardiogenic shock employed in previous real-world registry data as compared with trial definitions [6]. A recent study showed that ARF is the most common extra-cardiac complication (up to 43% patients) of patients affected by AMI-CS and it is burden by adverse outcome with an exponential fold increase with increasing number of other organs failure [7▪▪].

The adverse outcome in patients having cardiogenic shock and ARF has been also reported in other

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Curr Opin Crit Care 2021, 27:447–453
DOI:10.1097/MCC.0000000000000836

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KEY POINTS

- Respiratory failure requiring mechanical ventilation in patients with cardiogenic shock is frequent.
- Positive pressure ventilation may reverse hypoxemia and reduce transmural pressure favoring myocardial and end-organ perfusion and reducing left ventricular afterload.
- Mechanical ventilatory setting must be tailored on the cardiogenic shock etiopathology with particular caution in case of right ventricular failure and/or high preload dependency.
- A gap in data evidence exits regarding best ventilatory strategy in patients with cardiogenic shock.

studies. The AHEAD registry, in a population of unselected cardiogenic shock patients, demonstrated a mortality 69, 72, and 68% associated with the use of, respectively, NIV, mechanical ventilation or both which was significantly higher than patients not receiving mechanical ventilation (i.e., 40%) [8]. The overall mortality of patients with AMI-CS treated with mechanical ventilation was around 40% in several reports [9–12].

Heart–lung interactions

Although a comprehensive explanation of the the physiology and physiopathology of cardiopulmonary interactions associated with mechanical ventilation in patients with cardiogenic shock is beyond the scope of this review and it has been already published also in this journal [13,14], clinicians should be aware of a few basic physiological interactions.

Heart–lung interactions are based on the effects of changes in intrathoracic pressure (ITP) and lung volume on venous return and ventricular ejection. One of the principal determinant of venous return is the pressure gradient existing between the abdominal compartment and the right atrium (RA). In spontaneous breathing, venous return increases with physiological negative swings in ITP during inspiration, subsequently increasing right ventricular (RV) volume and causing the intraventricular septum to slightly move toward the left ventricle (LV). This will lead to a relative decrease in LV end-diastolic volume and compliance [15]. In patients without respiratory distress and without preload deficiency, these changes are clinically irrelevant. On the contrary, in those with increased respiratory effort (increase in respiratory rate or tidal volume) and/or with/without preload deficiency, these variations over the respiratory cycle will be empathized creating the pulsus paradoxus and potentially significant cardiac output (CO) alteration with hemodynamic impairment. To be remembered that however venous return is flow limited in considerably negative swings as ITP becomes markedly subatmospheric [16].

When positive pressure ventilation (PPV) is applied to ITP, the gradient between the RA and abdominal compartment decreases inducing a reduction in venous return and, consequently, in RV stroke volume [17,18]. However, the decrease is minimized by the concomitant increase in intra-abdominal pressure induced by abdominal wall muscle and diaphragmatic contraction [19–21].

These variations have to be taken into account in patients with severe hypovolemia and cardiogenic shock related to tamponade or RV dysfunction, where RV is even more preload-dependent and the addition of PPV may lead to an abrupt reduction of venous return, in addition to an afterload increase, and dramatically worsen the hemodynamic.

Conversely the positive end-expiratory pressure (PEEP) may have positive effect on the LV hemodynamic. Mechanical ventilation provide an increase in oxygenation, decreases preload unloading the congested heart [22] and reduces LV oxygen demand improving oxygen delivery to the ischemic myocardium [23], as evidenced by a decreased intracardiac lactate production, induces reversal of hypoxia-related pulmonary vasoconstriction, decreases work of breathing and overall metabolic demand [24]. In addition, PEEP acts also on LV afterload by decreasing transmural (or transthoracic) pulmonary pressure, and thus favoring the LV ejection [25–27] (Fig. 1).

Pathophysiology of respiratory failure in cardiogenic shock

Cardiogenic pulmonary edema is the usual cause of respiratory failure in patients experiencing cardiogenic shock. The most common profile of patients with cardiogenic pulmonary edema (CPE) and cardiogenic shock is the 'wet-cold' phenotype, characterized by low cardiac index, increased systemic vascular resistances, and pulmonary capillary wedge pressure. This phenotype accounts for nearly two thirds of patients with MI-associated cardiogenic shock and the majority of advanced decompensated heart failure and it is burden by the highest mortality as compared with patients presenting without congestion (dry) or without alteration in tissue perfusion (warm) [6,28▪].

In normal lungs fluid and solutes filtered from the circulation into the alveolar interstitial space do

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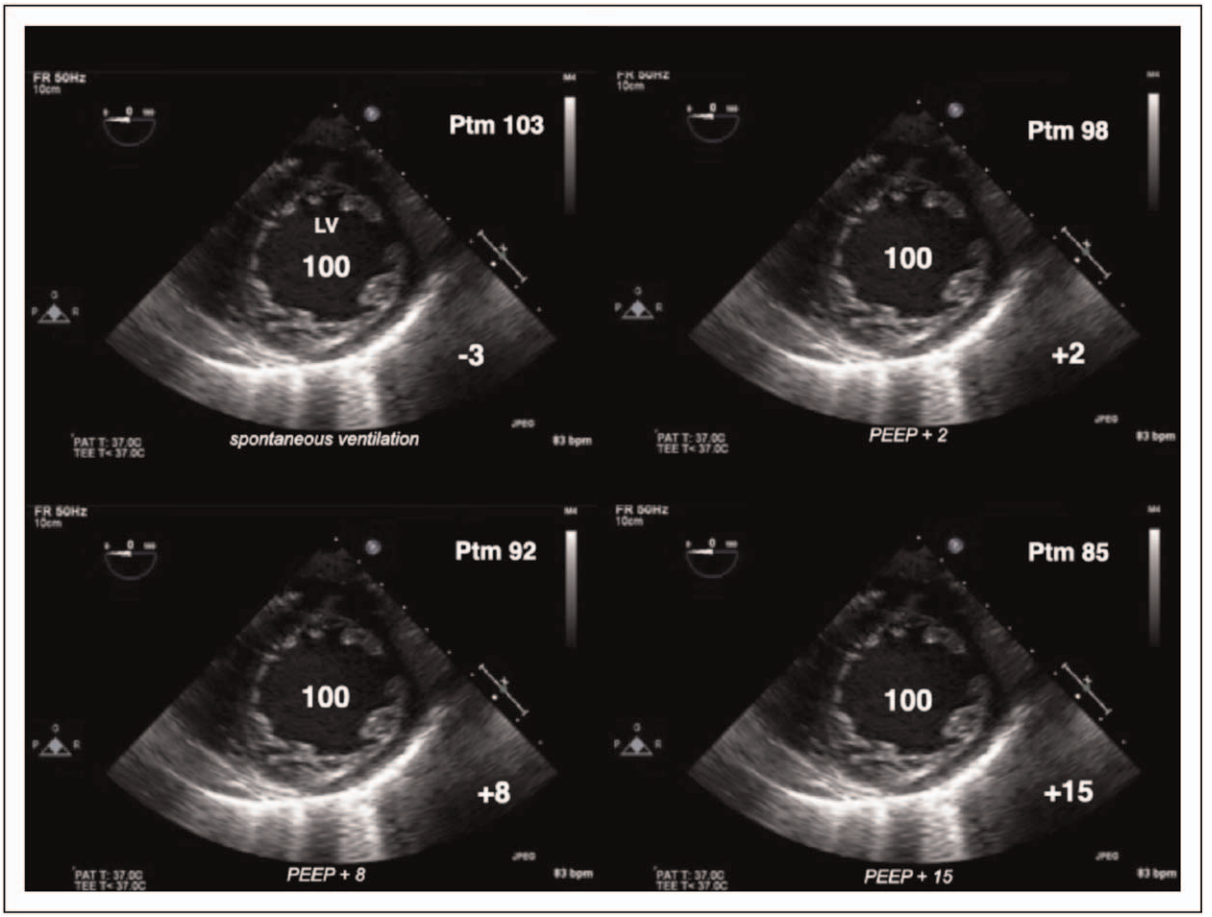

FIGURE 1. Schematic representation of relation between intrathoracic pressure and transmural pressure (calculated as intracavitary – extra cavitary pressure). Intracavitary pressure (left ventricle) is approximated to 100 mmHg for simplicity. During respiratory negative swing in spontaneous ventilation (−3) transmural pressure becomes more positive [transmural pressure = 100 − (−3) = 103], whereas applying exponential positive end-expiratory pressure levels (from top right to bottom) Ptm reduces accordingly (transmural pressure = 100 − 2 = 98).

not enter the alveoli because of very tight junctions of alveolar epithelium and most of the filtered fluid in the interstitial space is returned into the systemic circulation by the lymphatics. The hydrostatic force for fluid filtration across the lung microcirculation is approximately equal to the hydrostatic pressure in the pulmonary capillaries, which is partially balanced by a protein osmotic pressure gradient [29].

The rapid increase in hydrostatic pressure in the pulmonary capillaries, altering the capacity of fluid reabsorption, is secondary to the rise in left atrial and LV end-diastolic pressures (respectively, LAP and LV-EDP). Although preexisting cardiac conditions may result in chronically elevated LAP, for LAP values above 25 mmHg alveolar flooding usually occurs [29]. In addition, the concurrent inflammatory response may change vascular membrane permeability and further contribute to the development of alveolar edema. Consequently, the excess of interstitial and alveoli fluid results in a significant reduction of gas exchange and a concomitant ventilation–perfusion mismatch (shunt effect) related also to pulmonary hypoperfusions [30▪▪]. The resulting hypoxia, in face of increased metabolic O_2 demand and reflex sympathetic hyperactivation, reiterates myocardial ischemia, sustaining the deleterious ischemic vicious cycle worsening end-organ hypoperfusion, decreasing central oxygen content and ultimately resulting in multiorgan failure [6]. Preexisting conditions, such and chronic obstructive pulmonary disease or concomitant infectious or inflammatory processes may exacerbate or further worsen gas exchange and heart–lung interactions [14].

NONINVASIVE VENTILATION IN CARDIOGENIC SHOCK

Studies in patients with acute cardiogenic pulmonary edema have shown NIV to improve hemodynamics and reduce the intubation rate with acute systolic heart failure and pulmonary edema

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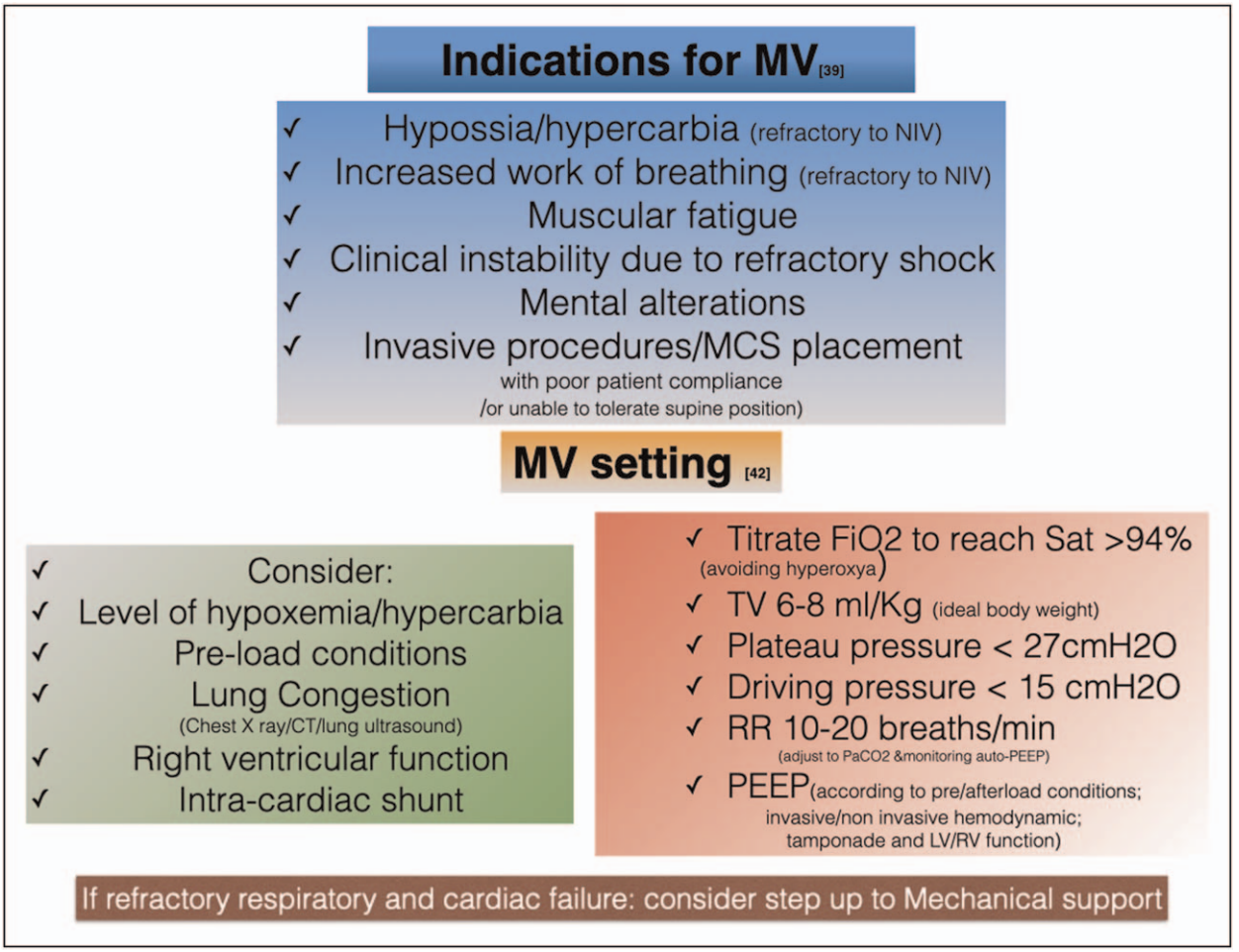
Indications for MV[39]
✓ Hypossia/hypercarbia (refractory to NIV)
✓ Increased work of breathing (refractory to NIV)
✓ Muscular fatigue
✓ Clinical instability due to refractory shock
✓ Mental alterations
✓ Invasive procedures/MCS placement
with poor patient compliance
/or unable to tolerate supine position)
MV setting [42]
✓ Consider:
✓ Level of hypoxemia/hypercarbia
✓ Pre-load conditions
✓ Lung Congestion
(Chest X ray/CT/lung ultrasound)
✓ Right ventricular function
✓ Intra-cardiac shunt
✓ Titrate FiO2 to reach Sat >94%
(avoiding hyperoxya)
✓ TV 6-8 ml/Kg (ideal body weight)
✓ Plateau pressure < 27cmH2O
✓ Driving pressure < 15 cmH2O
✓ RR 10-20 breaths/min
(adjust to PaCO2 &monitoring auto-PEEP)
✓ PEEP(according to pre/afterload conditions;
invasive/non invasive hemodynamic;
tamponade and LV/RV function)
If refractory respiratory and cardiac failure: consider step up to Mechanical support

FIGURE 2. Suggested evaluations in patient requiring mechanical ventilation. MV, mechanical ventilation; NIV, noninvasive ventilation.

compared with oxygen therapy alone, although controversial results on mortality have been reported demonstrated [31–35]. A meta-analysis of randomized clinical trials reported that continous positive end-expiratory pressure (CPAP) reduced mortality [relative risk (RR), 0.64; 95% confidence interval (CI), 0.44–0.92] and need for intubation (RR, 0.44; 95% CI, 0.32–0.66) compared with standard therapy. However, the studies reported were conducted on patients with acute cardiogenic pulmonary edema due to acute heart failure with or without cardiogenic shock. Based on the clinical results and pathophysiological beneficial mechanism, oxygen therapy and NIV, particularly CPAP, are part of the first-line therapy in patients experiencing acute heart failure (AHF) and cardiogenic shock [36] since prehospital setting [37,38].

Mechanical ventilation in cardiogenic shock

Decision to initiate mechanical ventilatory support is multifactorial, including level of hypoxemia (PaO_2/FiO_2) and hypercapnia, neurologic status, hemodynamic status, ability to protect the airway, RV dysfunction, and eventual required procedures (Fig. 2). Some data suggest that the requirement of mechanical ventilation in patient with acute coronary syndromes, as signs of higher acuity, are burden by higher mortality [39].

Best timing for endotracheal intubation has not been consistently addressed. However, a recent substudy of TRIUMPH trial, randomizing patients with refractory AMI-CS to a nitric oxide synthase inhibitor or placebo, demonstrated that each 1-h delay in mechanical ventilation initiation from the MI onset was independently associated with mortality in both univariate multivariate (OR, 1.03; 95% CI, 1.00–1.06) and sensitivity analysis (OR, 1.04; 95% CI, 1.01–1.06) [40▪▪].

There is lack of data also on specific agent to induce (for intubation) and maintenance of sedation. Considering the high risk of hemodynamic collapse during intubation, agents with reduced cardiovascular depressant action (such as etomidate, ketamine, or benzodiazepine) are suggested as well as reduction of sedation (both in term of dosage and

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administration time) to minimize the burden of ventilator-associated events [41,42].

In a recent study of relative small population (226 patients), comparing patient receiving NIV or mechanical ventilation basing on clinical indications, patients in the mechanical ventilation group were more often confused (83 vs. 31%, $P = 0.001$) had higher lactate levels (3.7 vs. 1.7 mmol/l, $P = 0.001$) and lower blood pressure (BP) with more frequent requirement of vasoactive medication (norepinephrine 88 vs. 69%, $P = 0.03$; dobutamine 61 vs. 27%, $P = 0.001$). In addition, patients treated with mechanical ventilation suffered from metabolic acidosis, more severe hypoxemia and hypercarbia more often and were treated with higher oxygen fraction at baseline compared with NIV group. In-hospital mortality was 45% in the mechanical ventilation group and 19% in the NIV group ($P = 0.01$), and 90-day mortality was 49 and 27% ($P = 0.03$), respectively. However, after adjustment for severity of disease using variables of the CardShock risk score, ventilation strategy had no influence on the 90-day outcome [43]. Higher severity of the parameters in mechanical ventilation group could be potentially related to greater acuity of patients.

A study investigating the prognostic factor and outcome of patients with complicated MI requiring mechanical ventilation demonstrated that nonsurvivors also presented greater incidence of cardiogenic shock ($P < 0.0016$), required more vasopressor support ($P < 0.028$), and suffered from a greater number of organ failures including more severe hypoxemia ($PaO_2/FiO_2 < 200$) [44].

A substudy of the IABP-SHOCK trial for attenuation of multiorgan failure reported a higher incidence of mechanical ventilation among patients without intra-aortic balloon pump (66.7 vs. 33.8%), although this not reached the statistical significance [45]. In addition, a study of patients admitted to ICU for AMI-CS divided by either receiving, on top of conventional treatment, IABP alone or IABP + mechanical ventilation showed a significant improvement in hemodynamic parameters in the latter group leading to higher rate of weaning rate from mechanical assistance ($P = 0.04$) and discharge ($P = 0.01$).

Ventilatory strategy and monitoring

There are no data (ND) regarding the best ventilatory strategy in patients with cardiogenic shock. The Protective Ventilation in Patients Without ARDS trial evaluated 961 intubated patients without ARDS, of whom 3–6% of patients had heart failure, demonstrated no difference in mortality, length of stay in the ICU, or ventilator complications when comparing low tidal volume (TV) (4–6 ml/kg) vs. intermediate TV (10 ml/kg) [46].

No 'best PEEP' strategy has been described as yet. A cautious assessment of cardiogenic shock underlying cause has to be performed, if feasible, before the application of PPV. In patients with RV dysfunction (or preload dependent hemodynamic profile, such as tamponade, hypovolemia, constriction) and accurate titration of PEEP should be performed to avoid further hemodynamic worsening related to excessive reduction of venous return or increased RV afterload. The minimal effective PEEP level (starting from 3 to 5 cmH_2O) should be preferred aiming the maintenance of adequate O_2 saturation and prevent atelectasis. Instead, in patients with predominant LV systolic dysfunction, particularly when associated with consistently elevated LAP, the level of PEEP can be started at 5–10 cmH_2O and be uptitrated as needed with close monitoring of gas exchange, hemodynamics (CO and mean arterial BP) [42], and bedside ultrasound to monitor lung recruitment and avoid hyperinflation [47,48] (Fig. 2).

Monitoring of respiratory function in mechanically ventilated patients with ongoing, or who are recovering, cardiogenic shock should include the evaluation and control of the spontaneous activity especially during sedation down-titration/held to avoid excessive negative ITP swings.

A crucial step is the withdrawal of positive pressure during the weaning. A seminal study by Lemaire *et al.* [49] from which significant pathophysiological mechanism understanding in the heart–lung interaction were inferred, demonstrated that patients with preexisting cardiac diseases, monitored over the withdrawal from PPV with esophageal pressure and Swan-Ganz catheter, were more prone to failed weaning from mechanical ventilation related to sudden increase in LAP and alteration of systolic–diastolic function. Weaning is accompanied by important changes in the cardiovascular and cardiopulmonary interaction. The discontinuation from PPV leads to sudden increased of venous return, sympathetic hyperactivation with catecholamine surge leading to increase heart rate (HR) and hypertension, O_2 supply reduction and work of breathing [50]. For these reasons, the spontaneous breathing trial in patients, especially those with cardiorespiratory comorbidities, should be carried and adequate treatment(s), including pre/afterload adjustment and HR titration, in patients demonstrating prognostic factor for weaning failure be titrated. A recent review has been published regarding pathophysiology of weaning and protocols applied [51▪].

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Mechanical ventilation in patients undergoing mechanical circulatory support

In case of refractory cardiogenic shock, mechanical circulatory support (MCS) has been increasingly used over the last decades. In a Nationwide Inpatient Sample analysis in the United States, an exponential increase of MCS utilization between 2004 and 2011 and the cardiogenic shock being the first indication for veno-arterial extracorporeal membrane oxygenation (VA-ECMO) in the ELSO registry [52,53]. However, ND are reported on the best ventilation strategy in this cohort of patients, with most of the indications deriving from the experience on patients with primary respiratory failure. Generally, lung protective strategy is applied as lungs contribute to a lesser extent to gas exchange when VA ECMO provides full assistance; therefore, tidal volume and minute ventilation should be reduced and PEEP titrated to reduce the risk of atelectasis. In addition, the presence of an artificial lung, allows to maintain low plateau and driving pressures reducing the RV afterload related to 'iatrogenic' increased ITP.

The LV afterload rise in VA ECMO may lead to LV overdistention, increased LV-EDP/LAP and the vicious cycle of acute pulmonary edema. Therefore, beside LV unloading strategies, PEEP titration, aiming at adequate arterial PaO_2 for organ perfusion, should be performed.

It has to be considered that the drainage from the venous side and the reduction of RV output may predispose to the conditions of pulmonary shunt and increased dead space. In patients with maintained alveolar ventilation but with low flow throughout the pulmonary vascular tree, there is risk of local hypocapnia, with consequent impaired alveolar fluid reabsorption and potentially bronchoconstriction [54,55].

Therefore, tight monitoring of gas exchange in patients undertaking VA ECMO considering that blood gas analysis may not be representative of the lung function, especially when full support is applied.

CONCLUSION

Mechanical ventilation is frequently required in patients experiencing cardiogenic shock. Pathophysiological mechanism and data regarding the management of ventilation derives by the extensive application of PPV in other cohort than cardiogenic shock patients. Further definition of the best ventilation interface and setting titrated on patients phenotypes represent a promising and necessary gap to be filled.

Acknowledgements

None.

Financial support and sponsorship

None.

Conflicts of interest

G.T. received fees for lectures by GE Healthcare, outside the present work.

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